ESPE NEWS

BRINGING THE LATEST IN PAEDIATRIC ENDOCRINOLOGY TO YOU

ESPE
European Society for Paediatric Endocrinology
Improving care of children with endocrine diseases by promoting knowledge and research

ISSUE 69 / *AUTUMN 2025*
ISSN 2045-5003 (ONLINE)

Approaches to diagnosis

Special issue **P5–10** >

Precision diagnostics in genetic obesity

From gene panels to whole genome sequencing and a look to the future **P5** >

Salivary cortisone: a role in diagnosis

Brian Keevil examines its value and importance **P6** >

Diagnosing severe primary IGF-1 deficiency

Elżbieta Petriczko gives insights into the challenging process of diagnosis **P7** >

Neuroimaging and pituitary disease

The imaging sequences most used in paediatric patients **P9** >

ALSO INSIDE:

News

ESPE appoints first CEO, plus ESPE grant has new convenor **P2** >

Summer School success, Yearbook 2025, ESPE's EDC campaign continues, plus ESPE e-Learning **P3** >

Our thanks to Anita **P10** >

Hot topics

The latest research **P4** >

Events and diary

Future meetings, dates and deadlines **P11** >

Keep up to date with ESPE events and deadlines!

Welcome

Autumn normally sees our Annual Meeting, but, having enjoyed the Joint Congress in May (with almost 8000 attendees and over 3300 abstracts), we must eagerly await the 64th Annual ESPE Meeting next September. Of course, ESPE doesn't rest, and there are many other ESPE activities. We are also excited to welcome ESPE's new Chief Executive Officer, Kay Miller.

This issue is dedicated to diagnosis in paediatric endocrinology. Improvements in our understanding frequently lead to the development of new approaches. Here, we look at the latest techniques for a range of disorders, making use of methods based on genetics, biochemistry and neuroimaging.

On **page 5**, Joanna Lerner, Lea Schmid, Stefanie Zorn and Martin Wabitsch consider the diagnosis of genetic obesity. Their review covers the selection of individuals for testing, the methods to use, and ways of improving diagnosis. They highlight how understanding the underlying genetics supports therapeutic decision making.

Taking salivary cortisone measurements can offer advantages in the diagnosis of disorders in children, as Brian Keevil explains on **page 6**. He looks at their use in the diagnosis of Cushing's disease and adrenal insufficiency, importantly explaining practical issues when using this approach.

Diagnosing severe primary IGF-1 deficiency presents a range of challenges. Elżbieta Petriczko examines these in detail on **page 7**, along with how to address them. Turn to her article for the chance to take part in a valuable survey on your experience of the IGF generation test.

Neuroimaging is often used to examine pituitary abnormalities in paediatric care. On **page 9**, Rayya Wael Musa Naffa', Sivakumar Manickam and Ulrike Löbel examine the most appropriate protocols, with informative examples of the resulting images.

The rest of the issue highlights the latest news from ESPE, including the imminent publication of the *ESPE Yearbook of Paediatric Endocrinology* (see **page 3**). We also take the opportunity to thank ESPE's retiring President, Anita Hokken-Koelega, for everything she has done for the Society (**page 10**). We welcome our new President, Mehul Dattani.

Antje Garten
Editor, *ESPE News*
Antje.Garten@medizin.uni-leipzig.de

Follow ESPE online...

Keep an eye on the latest ESPE news and activities at **www.eurospe.org**

You can also follow ESPE on Facebook, X and LinkedIn

/EuroSPE

ESPE

/EuroSPE

ESPE

Cover image:
Kehinde Olufemi Akinbo/ Shutterstock

YOUR SOCIETY

Welcoming Kay Miller

ESPE is delighted to welcome Dr Kay Miller FCMI CMgr as the Society's first Chief Executive Officer (CEO). Her leadership and expertise mark an exciting new chapter for ESPE.

Kay is an experienced leader in the scientific and medical international charity sector, with over 25 years of experience, including 22 years dedicated to medical membership organisations. She has held significant roles, including CEO of the Healthcare Infection Society and the Infection Prevention Society, and Strategy and Governance Consultant for the International Society for Respiratory Viruses.

Kay's career is marked by her expertise in managing organisational efficiency, developing strategic plans, and leading teams to achieve transformational success. She has a strong background in governance, financial management, membership growth and retention, and team development. Her passion for education and professional development has driven her to create and implement many successful educational programmes for nurses, trainees and consultants.

"I am thrilled to have been appointed as ESPE's first CEO. I hope to bring my experience and passion for growing medical membership organisations to the Society, and to build on the already excellent and impactful work of the ESPE Council and Committees. I look forward to meeting (and learning from) ESPE members at events in the very near future." **Kay Miller**

Kay Miller

Find out more

GRANTS

New convenor

Thomas Edouard

We welcome Thomas Edouard as the new convenor for the ESPE Visiting Professorship of Rare Diseases Grant. Professor Edouard leads the Endocrine, Bone Diseases and Genetics Unit at Children's Hospital in Toulouse, France. He also co-ordinates the reference centres for rare diseases of growth and bone (part of ERN-BOND).

He says, 'I am delighted to be taking on this role. The grant is vital in fostering international collaboration and advancing research in paediatric endocrinology. This initiative not only supports scientific renewal but also strengthens long-term partnerships that drive meaningful progress in rare disease care.'

Learn about the grant

EVENTS

Attendees at the ESPE Summer School 2025

Success for Summer School

ESPE Summer School 2025 took place at the picturesque Konventum, on the peaceful Danish coast at Helsingør on 7–9 May. This perfect setting saw 3 days of intensive learning and lively discussion. The outstanding programme had been compiled in record time, since Summer School 2024 took place just 6 months previously.

We thank our hosts, Katharina Main and YES representative Pernille Badsberg Norup, whose meticulous organisation ensured that the entire event ran smoothly. A total of 26 enthusiastic students from 14 countries joined with 14 expert faculty members. The social evening was a highlight, with a boat ride to see the famous statue of the Little Mermaid.

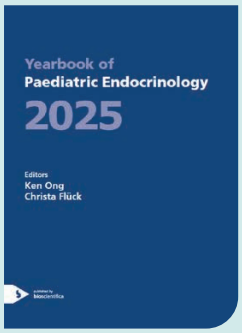
Feedback reflected a keen interest in more small-group, case-based discussions led by faculty, moving towards a problem-based learning approach. We look forward to incorporating this into next year's programme.

***Raja Padidela**, ESPE Summer School Co-ordinator*

Watch out for details of the next event in September 2026

RESOURCES

New Yearbook coming soon



Members can look forward to publication of the *ESPE Yearbook of Paediatric Endocrinology 2025* in late September.

Divided into 15 chapters, this valuable resource for paediatric endocrinologists covers recent advances in basic, translational and clinical research, as well as in clinical practice. You will be able to access it free of charge at the website below.

The Yearbook is a collaborative project among experts in specific fields, who search the literature for the most relevant articles and write short commentaries. We are grateful to them for their important role in supporting this ESPE activity.

***Christa Flück and Ken Ong**, Editors*

Find all Yearbooks since 2018

YOUR SOCIETY

Open letter to 27 EU states

During the summer, ESPE joined with the European Society of Endocrinology and the Endocrine Society to send an open letter to the 27 EU states, to address concerns that the EU is no longer on track to effectively ban endocrine-disrupting chemicals (EDCs) from our environment.

The letter was disseminated with the help of national paediatric and adult endocrine societies. It urges Member States to implement stricter measures and outlines the high economic costs of inaction. ESPE will continue to lobby policymakers until a regulatory framework is in place to protect children from harmful exposure.

Read the open letter

RESOURCES

Test yourself with e-Learning

The ESPE–ISPAD (International Society for Adolescent and Pediatric Diabetes) e-Learning web portal is an interactive resource on paediatric endocrinology and diabetes mellitus. Use it, free of charge, to expand your knowledge of paediatric endocrinology.

Find out more

Register for free access

This issue's clinical case highlight

A boy with delayed puberty

A 15-year-old boy was referred due to delayed puberty, complaining of small penis and testes and an absence of facial hair. His prenatal and natal history were unremarkable, but he had micropenis and undescended testes at birth.

On physical examination, the stretched penile length was 4.0cm. The left testis was soft, measured 0.7x1.0cm, and was within the scrotum; the right testis had a maximum diameter of 0.8cm and was identified at the left right inguinal ring. He had slight pubic hair growth (G1, PH2) and no axillary hair. He had a high-pitched voice, eunuchoid habitus and no facial hair. His growth pattern was normal without a growth spurt.

Follicle-stimulating hormone and luteinising hormone levels were undetectable, and testosterone was very low. He had an impaired sense of smell, and the olfactory test revealed he had anosmia.

What imaging test is best at this point in the investigation?

- ☐ Computed tomography
- ☐ Abdominal ultrasound
- ☐ Magnetic resonance imaging
- ☐ Skull radiogram

For the answer, see **page 11**.

ESPE e-LEARNING

Bringing you recent highlights from the world of research

Immunotherapy for type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM), which accounts for 5–10% of all diabetes cases worldwide, has shown an increase in both incidence and prevalence. The risk factors leading to development of T1DM comprise both genetic and environmental factors, such as viral infections, dietary patterns and exposure to specific chemicals.

Patients with T1DM require insulin treatment, which, however, does not target underlying autoimmune pathomechanisms. Early immunotherapy has been shown to be beneficial for maintaining β-cell function by promoting immune tolerance.

Salame *et al.* conducted a meta-analysis on the efficacy of different immunotherapies in paediatric patients with T1DM by measuring their average C peptide levels, daily dosage of insulin, and levels of glycated haemoglobin (HbA1c).

They concluded that although good results were achieved concerning HbA1c and C peptide levels and daily insulin dosage requirements, it was not possible to show that immunotherapy improves the two latter outcomes, demonstrating the need for further research to establish immunotherapy as a standard treatment.

Read the full article at Salame *et al.* 2025 *PLoS One*
https://doi.org/10.1371/journal.pone.0321727

The meta-analysis can also be found in the ***PROSPERO database***

A microRNA-based dynamic risk score for T1D

Since the approval of teplizumab for the prevention of type 1 diabetes mellitus (T1DM), there has been a surge in the advent of various strategies for screening individuals at high risk of developing the disease.

This study by Joglekar *et al.* has shown the development of a microRNA-based dynamic risk score (DRS) to identify individuals at high risk of T1DM. It used data from 2204 individuals across four countries (Australia, Denmark, Hong Kong and India). Fifty microRNAs linked to β-cell loss were identified and used to create a multicontext DRS, further enhanced by generative artificial intelligence.

The model effectively stratified risk of T1DM (area under the curve=0.84) in a validation set (n=662) and predicted insulin needs post-islet transplantation. In a clinical trial, baseline microRNA, not clinical data, distinguished responders to imatinib. The approach shows promise for prediction of T1DM risk and treatment efficacy.

Read the full article at Joglekar *et al.* 2025
Nature Medicine
https://doi.org/10.1038/s41591-025-03730-7

Oral infigratinib for children with achondroplasia

This phase 2 open-label clinical trial evaluated the safety and efficacy of oral infigratinib, an FGFR1–3 inhibitor, in children aged 3–11 years with genetically confirmed achondroplasia. Achondroplasia, caused by activating *FGFR3* mutations, results in severe disproportionate short stature.

Savarirayan *et al.* reported that infigratinib, administered once daily for 6 months, demonstrated dose-dependent improvements in annualised height velocity (AHV), with the highest dose group achieving an AHV of 3.38cm/year over baseline. Importantly, proportional body ratios (upper-to-lower segment) improved, suggesting that treatment may promote more physiologic linear growth. Adverse events were mostly mild or moderate; the most common included increased serum creatinine and hyperphosphataemia, consistent with FGFR inhibition. No treatment discontinuations occurred due to side effects. The results support the potential of targeted oral FGFR inhibition as a therapeutic option in achondroplasia, offering an alternative to injectable therapies such as vosoritide.

Further studies, including a randomised phase 3 trial, are ongoing to assess long-term outcomes, optimal dosing and impacts on functional parameters and quality of life.

Read the full article at Savarirayan *et al.* 2025
New England Journal of Medicine
https://doi.org/10.1056/NEJMoa2411790

Carbohydrate-restricted diet and β-cell response

It is well known that insulin secretion is compromised in those with type 2 diabetes mellitus (T2DM) and that this may, in part, be related to the excessive consumption of carbohydrate. Gower *et al.* compared eucaloric carbohydrate-restricted (CR) and high-carbohydrate (HC) diets in adult individuals with T2DM. Hyperglycaemia clamps were used to assess C-peptide response to glucose at baseline and after 12 weeks of a controlled diet. An oral glucose tolerance test (OGTT) was performed to measure disposition index.

At 12 weeks, those on the CR diet had a twofold greater acute C-peptide response than those on the HC diet (P<0.01). The effect of diet on maximal C-peptide release was specific to European Americans (again greater with the CR diet, P<0.01). OGTT results showed a 32% higher disposition index in those receiving the CR diet.

The results suggest that a CR diet may have beneficial effects on β-cell function, even without restricting calories, in those with T2DM.

Read the full article at Gower *et al.* 2025
Journal of Clinical Endocrinology & Metabolism
https://doi.org/10.1210/clinem/dgae670

Precision diagnostics in genetic obesity

The authors consider approaches from gene panels to whole genome sequencing and look to future developments.

Joanna Lerner

Lea Schmid

Stefanie Zorn

Martin Wabitsch

Disease-causing genetic alterations that lead to abnormal regulation of hunger and satiety (hyperphagia) in the hypothalamus can cause early-onset, severe forms of obesity. Many genes associated with genetic obesity are involved in the leptin–melanocortin pathway. This is the main regulatory circuit in the hypothalamus responsible for regulating hunger, satiety, energy homeostasis and body weight.

Although severe early-onset obesity and hyperphagia are hallmarks of genetic obesity, these forms are often difficult to distinguish from common obesity in clinical practice. Genetic testing is crucial in the clinical care of individuals with obesity because:

(1) identifying an underlying genetic cause potentially relieves patients and their families
(2) it guides the use of mechanism-based treatments, such as metreleptin and setmelanotide, which are available for certain forms of monogenic obesity
(3) it supports careful decision-making regarding bariatric surgery, and
(4) it advances research that offers new insights into the underlying signalling pathways and functional impact of gene variants.[1]

Identifying individuals for genetic testing

International guidelines recommend genetic testing in minors with severe obesity (body mass index (BMI) ≥35kg/m² or ≥120% of the 95th percentile) before the age of 5 years who show clinical features of genetic obesity, particularly extreme hyperphagia and/or a family history of severe obesity.[2]

A recent multicentre observational study showed that monogenic obesity due to biallelic variants in certain genes can be distinguished from common obesity at as early as 6 months of age, and suggests a BMI ≥24kg/m² at the age of 2 years as a threshold for genetic testing in suspected cases.[3]

Genetic tools and strategies for diagnosis

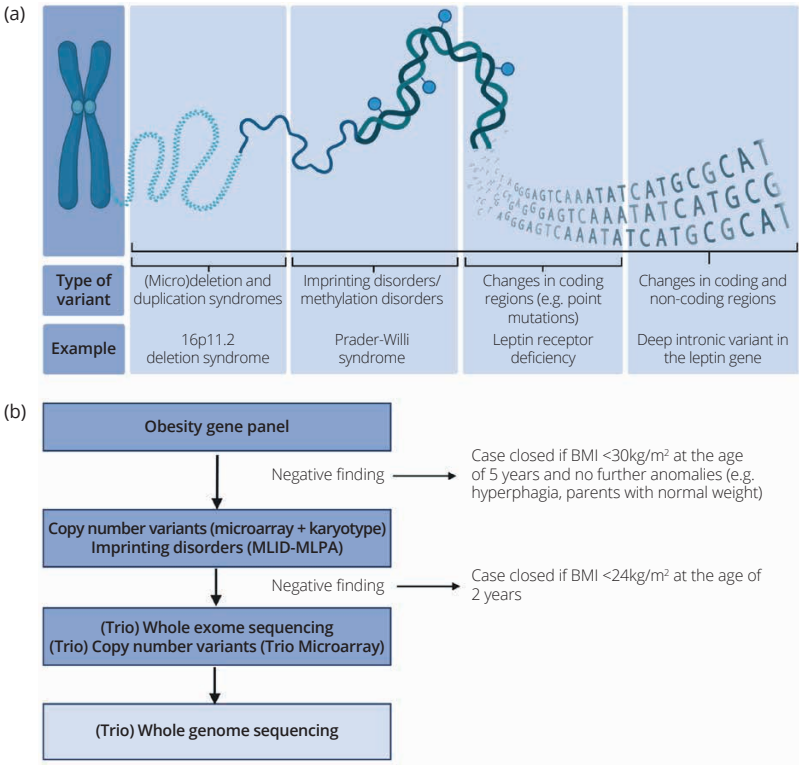
Genetic testing offers various methods to investigate the possible underlying genetic causes of severe obesity, which can be applied in a stepwise diagnostic approach if needed.

A 'panel' refers to a list of genes associated with a specific disease, compiled through comprehensive literature reviews and database searches. In the context of obesity, such panels typically include genes whose products directly affect the leptin–melanocortin pathway. If no causative variant is found despite strong clinical suspicion, or if obesity is accompanied by additional phenotypic features (e.g. ocular or renal disorders), expanding the gene panel or performing whole-exome analysis may be warranted. Genes analysed through this approach may affect the leptin–melanocortin pathway as part of a broader pathophysiological mechanism.

The detected variants can be classified into five categories according to the guidelines of the American College of Medical Genetics and Genomics, ranging from benign to pathogenic.[4] If the currently available information is insufficient to evaluate pathogenicity, the variant should be re-evaluated after 3–5 years in order to incorporate new findings into the variant classification.[5]

Copy number variants, such as 16p11.2 microdeletions, along with imprinting disorders, such as Prader–Willi syndrome, are further genetic causes of obesity that must be considered in diagnostics. Since the assessment of identified genetic variants primarily relies on the clinical information provided, the accuracy of genetic testing can be improved by offering comprehensive clinical details. Diagnostic yield may be further increased by the inclusion of the biological parents of the affected individual in the form of a trio-analysis.

A possible stepwise approach to genetic testing for obesity, as implemented by Ulm University Medical Center, is presented in the Figure.



(a) Examples of human genetic causes of obesity (created with Biorender, https://www.biorender.com). (b) Stepwise approach to genetic testing for obesity as implemented by the Ulm University Medical Center. MLID, multi-locus imprinting disturbance; MLPA, multiplex ligation-dependent probe amplification.

Continued on page 6

Continued from page 5

Human genetic diagnostics supports therapeutic decision making, particularly regarding available targeted, mechanism-based pharmacological treatments"

Recommendations for improving diagnosis

Close collaboration between clinicians, institutes of medical genetics and specialised centres for genetic obesity enables precise evaluation of genetic findings and therapeutic guidance. In this context, other methods may be initiated (such as whole-genome sequencing which includes non-coding DNA regions), particularly in cases with strong clinical suspicion and previously negative genetic testing.

Using the full range of human genetic methods in obesity research has led to the identification of additional obesity-associated genes and signalling pathways, such as the *ASIP* and *HTR2C* genes.[6,7] However, despite technical and scientific progress, many cases of suspected genetic obesity remain undiagnosed.[5]

In conclusion, human genetic diagnostics enables the identification of genetic causes of obesity and supports therapeutic decision making, particularly regarding available targeted, mechanism-based pharmacological treatments. Genetic testing should always be guided by clinical criteria and may involve a range of methods tailored to the individual's presentation.

Joanna Lerner, Lea Schmid, Stefanie Zorn and Martin Wabitsch

Division of Paediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, German Center for Child and Adolescent Health (DZKJ), Ulm University Medical Center, Germany

References

1. Hinney *et al.* 2022 *Nature Reviews Endocrinology* https://doi.org/10.1038/s41574-022-00716-0.
2. Styne *et al.* 2017 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/jc.2016-2573.
3. Zorn *et al.* 2025 *Lancet Child & Adolescent Health* https://doi.org/10.1016/S2352-4642(25)00065-3.
4. Richards *et al.* 2015 *Genetics in Medicine* http://doi.org/10.1038/gim.2015.30.
5. Morandi *et al.* 2024 *Pediatric Obesity* https://doi.org/10.1111/ijpo.13183.
6. Kempf *et al.* 2022 *Nature Metabolism* https://doi.org/10.1038/s42255-022-00703-9.
7. He *et al.* 2022 *Nature Medicine* https://doi.org/10.1038/s41591-022-02106-5.

Salivary cortisone as a diagnostic marker

Brian Keevil examines the importance of these measurements in paediatric patients.

Brian Keevil

Salivary cortisone has the advantage of detection when serum cortisol levels are low, as well as no interference from oral hydrocortisone"

Why measure salivary cortisone?

Cortisol is inactivated to cortisone in the salivary gland by 11β-hydroxysteroid dehydrogenase type 2 and, as a result, concentrations of cortisone in saliva correlate strongly with serum cortisol concentrations. The free biologically active hormone is measured in saliva which, unlike serum cortisol, leaves salivary cortisone concentrations unaffected by changes in cortisol-binding globulin. Salivary cortisone is also superior to salivary cortisol because it is not affected by contamination from oral hydrocortisone medication.

Cortisone may also be a preferable measure in children, as cortisol is often undetectable. However, in agreement with previous studies, age may also be an important factor in the interpretation of early morning cortisone measurements in children.

Salivary cortisol and cortisone are measured simultaneously in the same liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay[1] and can be used to assess cortisol excess, deficiency and hydrocortisone replacement, with salivary cortisone having the advantage, as mentioned, of detection when serum cortisol levels are low.[2]

The advantages of using saliva samples are well known, and include convenient home collection, savings in clinic and phlebotomy time, usefulness in needle-phobic patients and less time off school and work for carers.

Saliva samples are easy to collect using commercial swabs. These are simple to use and well-tolerated by children, but may present a choking hazard in smaller infants, where a modified swab can be inserted into a pacifier or held in the hand to prevent choking. Sufficient saliva for cortisone analysis can be collected in under 4 minutes. Salivary cortisol and cortisone are stable for at least 72 hours at room temperature or for more than a week at 4°C.[3]

Cushing's syndrome

Late-night salivary cortisol/cortisone is already in routine use for the challenging diagnosis of Cushing's syndrome (CS). Bedtime salivary cortisol measured by LC-MS/MS can also be applied as a screening test for CS in children. Age- and sex-specific cut-off levels were found not to be necessary; results showed that salivary cortisol and cortisone could be used interchangeably.[4]

The other commonly used test for CS is the overnight dexamethasone suppression test (ONDST), and salivary cortisone can now be used rather than serum cortisol,[5] as confirmed in a follow-up adult study. Currently, the ONDST necessitates an overnight stay in hospital, whereas using the saliva test enables the patient to take the dexamethasone at home the night before and then to post the morning saliva sample to the laboratory. This could be particularly useful in paediatric practice, but has not yet been attempted.

Adrenal insufficiency

Recent work has shown that waking salivary cortisone (WSC) could be important in diagnosing adrenal insufficiency,[6] where it has been demonstrated to be an accurate screening test. WSC was shown to reduce the need for synacthen testing by up to 70%, and thus has the potential to reduce costs.

This novel work has been confirmed in a follow-up study, indicating that many adults and possibly also children with normal adrenal function are being subjected to expensive and unnecessary synacthen tests. The Salivary Cortisone as an Adrenal Insufficiency Test (SCAIT) junior study is the first to evaluate the use of WSC in children. Preliminary work shows that paediatric cut-offs may be different to those recently reported in adults. More work is needed to refine these.[7]

The early-morning peak in cortisol secretion gradually emerges from birth onwards to form a stable morning/

Continued on page 7

Continued from page 6

evening ratio from the age of 6–9 months.[8] These results agree with the SCAIT study, and imply that age related cut-offs will be necessary for WSC. Nevertheless, home WSC has the potential to improve the diagnostic pathway for adrenal insufficiency, to reduce false-positive screen results and to enable more tailored diagnostic testing.

Issues in sampling

Following adrenocorticotrophin (ACTH) stimulation, cortisone and cortisol concentrations are maximal upon waking, and collection time standardisation is crucial. Later sampling shows more variability, as ACTH stimulation subsides and cortisol concentration falls.

This should be contrasted with the serum screening test performed at 08.00–09.30h used in clinical practice. In patients who rise early, cortisol levels may already be falling, giving a falsely low peak cortisol, and thus potentially subjecting them to more invasive definitive diagnostic testing. The serum test also exhibits variation in cut-off values, and this combined uncertainty renders it inaccurate for screening for adrenal insufficiency.

A service evaluation carried out to identify barriers to clinical implementation of WSC showed the principal challenge was reporting of results to clinicians, due to delays in reporting from the reference laboratory to the requesting laboratory. Currently, two UK centres routinely measure salivary cortisone, but more laboratories are taking up the LC-MS/MS method required for accurate results.

A research grant application has been made to enable this test to be rolled out across the NHS, and several UK laboratories are already at an advanced stage in developing this methodology.

The use of saliva samples to measure cortisol and cortisone in the investigation of the hypothalamic-pituitary-adrenal axis is gaining in popularity amongst adult endocrinologists. Cortisone is showing more promise than cortisol for reasons outlined, and perhaps deserves the greater focus. Salivary cortisone is undoubtedly a good test for both cortisol excess and deficiency states, but further work is needed to establish its use in paediatric practice.

Brian Keevil
Consultant Clinical Scientist for Biochemistry, Wythenshawe Hospital, Manchester University NHS Foundation Trust, UK

References

1. Perogamvros *et al.* 2010 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/jc.2010-1215.
2. Blair *et al.* 2017 *Current Opinion in Endocrinology, Diabetes & Obesity* https://doi.org/10.1097/med.0000000000000328.
3. Tonge *et al.* 2022 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgac419.
4. Ueland *et al.* 2021 *Journal of the Endocrine Society* https://doi.org/10.1210/jendso/bvab033.
5. Issa *et al.* 2023 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgad242.
6. Debono *et al.* 2023 *New England Journal of Medicine Evidence* https://doi.org/10.1056/EVIDoa2200182.
7. Kervezee *et al.* 2025 *Journal of Clinical Endocrinology & Metabolism* https://doi.org/10.1210/clinem/dgae590.
8. Tavernier *et al.* 2023 *Endocrine Abstracts* https://doi.org/10.1530/endoabs.95.OC5.9

Diagnosing severe primary IGF-1 deficiency

Elżbieta Petriczko examines the challenges in diagnosing this rare disease.

Elżbieta Petriczko

Severe primary insulin-like growth factor-1 (IGF-1) deficiency (SPIGFD) is a rare growth disorder characterised by short stature (standard deviation score (SDS)≤–3.0) and low circulating concentrations of IGF-1 (SDS≤–3.0) despite normal or elevated concentrations of growth hormone (GH). Laron syndrome is the best characterised form of SPIGFD, caused by a defect in the GH receptor (*GHR*) gene. Diagnosing SPIGFD can be challenging due to several clinical, biochemical and logistical issues, summarised as follows.

1. Rarity and low awareness

SPIGFD is rare, which limits clinician experience and awareness. It is often underdiagnosed or misdiagnosed as other growth disorders, such as GH deficiency (GHD).

2. Overlapping clinical features

Children with SPIGFD typically present with severe short stature (often >3 SD below mean), but similar phenotypes can occur in GHD, genetic syndromes (e.g. Noonan syndrome) or constitutional delay of growth and puberty. A lack of specific clinical signs makes it difficult to distinguish SPIGFD from other causes of growth failure.

> *Diagnosing SPIGFD requires a high index of clinical suspicion and a systematic, multidisciplinary approach"*

3. Biochemical complexity

IGF-1 levels: persistently low IGF-1 is a hallmark of SPIGFD, but IGF-1 can be affected by:

- nutritional status
- liver function
- thyroid disorders
- chronic illness
- age and pubertal stage.

GH levels: patients typically have normal or elevated GH levels, but GH stimulation testing is variable and not always standardised across centres.

IGF-binding protein-3 (IGFBP-3) and acid-labile subunit (ALS): levels may also be low but are not consistently used or available in all labs.

4. Variability in laboratory reference ranges

- IGF-1 and GH assays lack universal standardisation.
- Reference ranges vary by lab, assay method, age and sex, which complicates interpretation.
- Paediatric-specific normative data are especially lacking in some regions.

5. Genetic testing

Mutation of the following genes is associated with a range of characteristics:

IGFALS: Mutations lead to decreased serum ALS, resulting in impaired IGF-1 stabilisation and transport. They are associated with moderate short stature, delayed puberty and low IGF-1 levels.

GHR: Mutations are the classic cause of Laron syndrome, a prototypical form of SPIGFD. It is characterised by severe short stature, normal/high GH and markedly low IGF-1.

Continued on page 8

Continued from page 7

Differential diagnosis of severe short stature with low IGF-1

Category	Condition	GH levels	IGF-1 levels	Key features/clues
Primary IGF-1 deficiency	SPIGFD (e.g. Laron syndrome)	Normal or ↑	↓↓↓	Severe short stature, GH resistance, familial cases
GH deficiency	Isolated GHD, MPHD	↓↓↓	↓↓	Pituitary abnormalities, midline defects, hypoglycaemia
Chronic disease	Coeliac, renal failure, inflammatory disease	Variable	↓	Symptoms of systemic disease, labs for underlying cause
Nutritional	Malnutrition, anorexia	↓ or normal	↓	Low weight-for-height, dietary history
Genetic syndromes	Noonan, Turner, SHOX deficiency	Normal or ↓	↓ or normal	Dysmorphic features, karyotyping or gene testing helpful
Constitutional delay	CDGP (normal variant)	Normal	Normal or ↓	Bone age delay, family history of delayed puberty
Endocrine disorders	Hypothyroidism, Cushing's, diabetes	Variable	↓	Abnormal thyroid or cortisol labs

CDGP, constitutional delay of growth and puberty; MPHD, multiple pituitary hormone deficiency.

IGF1: Homozygous mutations are very rare and associated with extremely low IGF-1 levels, severe pre- and postnatal growth failure, sensorineural deafness and insulin resistance.

STAT5b: Mutations cause severe GH resistance with low IGF-1, growth failure and profound immune dysfunction due to the protein's role in cytokine signalling.

NFKBIA: This encodes IκBα, a regulator of NF-κB signalling. Mutations can cause growth failure along with immune deficiency (e.g. ectodermal dysplasia with immunodeficiency).

PAPPA2: This encodes a protease that releases IGF-1 from IGFBPs. Mutations result in functional IGF-1 deficiency despite normal or elevated total IGF-1, and are associated with short stature and sometimes insulin resistance.

PTPN11: Activating mutations impair GH signalling by dephosphorylating STAT5b, leading to partial GH insensitivity (also implicated in Noonan syndrome).

6. Nutritional and chronic disease confounders

Malnutrition and chronic systemic diseases (e.g. coeliac disease, renal disease) can lead to secondary IGF-1 deficiency. Distinguishing primary versus secondary IGF-1 deficiency requires thorough exclusion of other conditions.

7. Lack of consensus guidelines

There is no universally accepted diagnostic algorithm for SPIGFD. Criteria may vary between regulatory authorities (e.g. the European Medicines Agency (EMA) versus the US Food and Drug Administration). For example, EMA defines SPIGFD as: height SDS<–3, IGF-1 SDS<–3, GH level >10ng/ml (after stimulation), but these cutoffs are debated and not always practical.

8. Delayed dagnosis

Due to the above challenges, diagnosis is often delayed until late childhood. This reduces the window for effective treatment (e.g. recombinant human IGF-1 therapy), which is most beneficial when started early.

Conclusion

Diagnosing SPIGFD requires a high index of clinical suspicion and a systematic, multidisciplinary approach. The process involves:

- thorough exclusion of secondary causes of growth failure, such as chronic systemic illness, malnutrition, endocrine disorders or psychosocial factors
- detailed biochemical evaluation, including persistently low IGF-1 levels in the context of normal or elevated GH levels
- genetic testing to identify underlying molecular defects (e.g. mutations in *GHR*, *IGF1*, *STAT5b* or related genes) which can confirm the diagnosis and inform prognosis and treatment planning.

Key barriers to accurate diagnosis include:

- limited awareness of SPIGFD among general paediatricians and even endocrinologists
- overlapping phenotypes with other growth disorders
- variability in laboratory reference standards and access to specialised testing
- lack of standardised diagnostic algorithms across institutions or regions.

Elżbieta Petriczko
Department of Pediatrics, Endocrinology, Diabetology, Metabolic Disorders of Developmental Age, Pomeranian Medical University in Szczecin, Poland

Further reading

- Nguengang Wakap *et al.* 2020 *European Journal of Human Genetics* https://doi.org/10.1038/s41431-019-0508-0.
- Cohen *et al.* 2014 *Drugs in R&D* https://doi.org/10.1007/s40268-014-0039-7.
- Petriczko *et al.* 2019 *Endokrynologia Polska* https://doi.org/10.5603/ep.a2018.0074.
- Bauskis *et al.* 2022 *Orphanet Journal of Rare Diseases* https://doi.org/10.1186/s13023-022-02358-x.
- Backeljauw *et al.* 2013 *Hormone Research in Paediatrics* https://doi.org/10.1159/000351958.
- Bang *et al.* 2021 *European Journal of Endocrinology* https://doi.org/10.1530/eje-20-0325.

Share your experience of the IGF generation test in diagnosing SPIFGD
Take part in a short survey (<5 minutes) on unmet needs and barriers to diagnosis
COMPLETE THE SURVEY by 30 November 2025

Neuroimaging in endocrinology

The authors review the imaging sequences that are most frequently used to assess paediatric pituitary disease.

Rayya Wael Musa Naffa'

Sivakumar Manickam

Ulrike Löbel

Neuroimaging, and magnetic resonance imaging (MRI) in particular, is frequently used in children with endocrinopathies to identify pituitary abnormalities and exclude associated intracranial malformations. The pituitary gland, consisting of the anterior adenohypophysis and posterior neurohypophysis, is such a small structure that it requires specific MRI protocols to adequately assess pituitary pathologies.

Imaging protocols

At our hospital, the standard pituitary protocol includes the following sequences (Figure 1): sagittal T1-weighted (T1W) spin-echo (SE), coronal T2W SE and a 3D SPACE/DRIVE/FIESTA/CISS, which is a high-resolution 3D sequence that allows images to be reconstructed in multiple planes (its heavy T2-weighting maximises the contrast between brain parenchyma and cerebrospinal fluid).

If a patient receives contrast (useful to depict a pituitary tumour or confirm a Rathke cleft cyst), additional T1W images are obtained in sagittal and coronal planes (Figure 1). Apart from the 3D technique (which uses 1-mm isotropic voxels), a 2-mm slice thickness and a field of view (FOV) focusing on the pituitary gland (FOV 140mm, matrix 256×256) are used. This allows high in-plane resolution, but the sequences do not usually cover the whole head.

To exclude co-existing brain malformations, it is useful to add conventional brain images such as axial T2W (in children there is typically a 4-mm slice thickness, a repetition time (TR) of ~4000–5000ms, an echo time (TE) of ~100–120ms, FOV ~210–230 mm, matrix ~320×320, 10% gap) and a 3D T1W SPGR/MPRAGE (1.0–1.2mm isotropic voxels). 3D T1 MPRAGE typically provides enough image resolution to identify an ectopic posterior pituitary gland or to confirm the absence of the posterior bright spot and stalk thickening in Langerhans cell histiocytosis. Standard brain images typically also include diffusion-weighted imaging (DWI) to exclude acute changes and fluid attenuated inversion recovering (FLAIR) images.

Another imaging technique that may be used is dynamic contrast-enhanced T1W imaging. The technique uses sequential coronal frames at 30, 60, 90, 120, 150 and 180s after injection of a gadolinium-based contrast agent (~0.05mmol/kg) to capture contrast dynamics (wash-in/wash-out) of microadenomas, as microadenomas often show delayed enhancement and may be obscured in conventional post-contrast scans. Typical parameters are: slice thickness 3mm, 0.6-mm gap, TE ~8–12ms, TR ~500–600ms, small FOV (160×160mm), matrix 256×256, number of excitations (NEX) 3–5, turbo factor 3. In a 2023 study, 3D high-resolution fast spin-echo (FSE) sequence combined with dynamic contrast significantly improved microadenoma detection in Cushing's disease compared with 2D FSE, with sensitivity climbing from ~66% (2D) to ~80% (3D SPGR), and even higher with FSE.[1]

Some novel techniques have recently been employed in adults. Post-contrast CISS/FIESTA-C imaging[2] and ultra high field 7T MRI (0.3-mm isotropic voxels) in Cushing's disease showed higher lesion detection rates compared with standard imaging.[3] In addition, photon counting computed tomography (CT) accurately identified 92% of intraoperatively confirmed adenomas, compared with 56% by contrast-enhanced MRI.[4]

Clinical examples

Analysing the pituitary using MRI[5] includes assessing the:

- anterior lobe: size/configuration (dependent on patient age and pubertal status; convex in newborns, enlarged from puberty) and signal (isointense on T1W/T2W; normal T1W hyperintensity in neonates)
- posterior lobe: normal T1W hyperintense signal due to presence of vasopressin, normal location (versus ectopia)
- pituitary stalk: intact, thickness under 2mm, with possible deviation.

In microadenomas, the signal intensity on MRI varies from case to case, as components such as water are not constant between pituitary adenomas, and modifications such as degeneration, haemorrhage and infarction also develop. T1W images often show a mild hypointensity compared with the normal gland, but lesions may be isointense. In contrast, T2W images show a variety of signal intensities from low to high compared with the normal

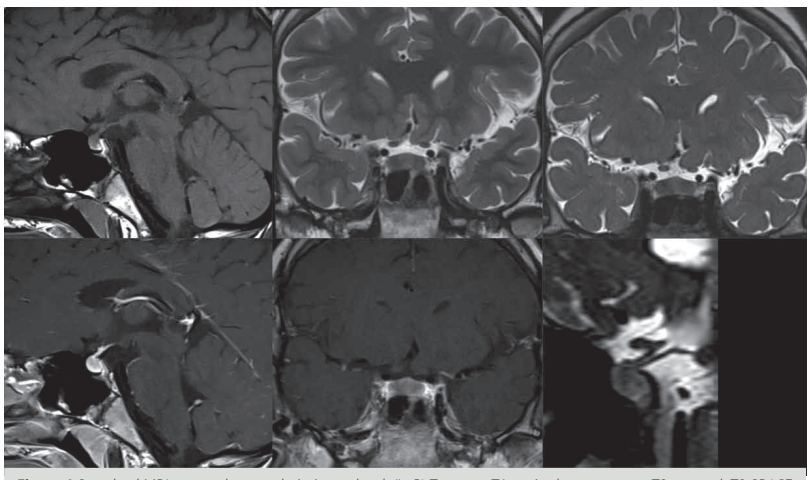


Figure 1 *Standard MRI protocol, normal pituitary gland. (L–R) Top row: T1 sagittal pre-contrast; T2 coronal; T2 SPACE coronal. Bottom row: post-contrast T1 sagittal and coronal; T2 SPACE reconstructed sagittal image.*

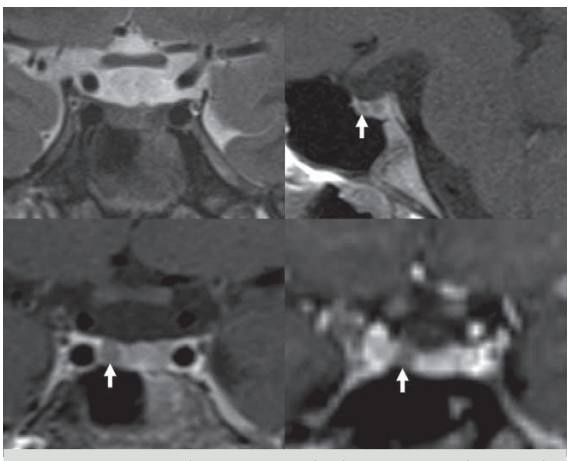


Figure 2 *Pituitary microadenoma. (L–R, top then bottom) T2 coronal, T1 sagittal and coronal post-contrast, dynamic post-contrast sequences (one selected time point).*

Continued on page 10

Continued from page 9

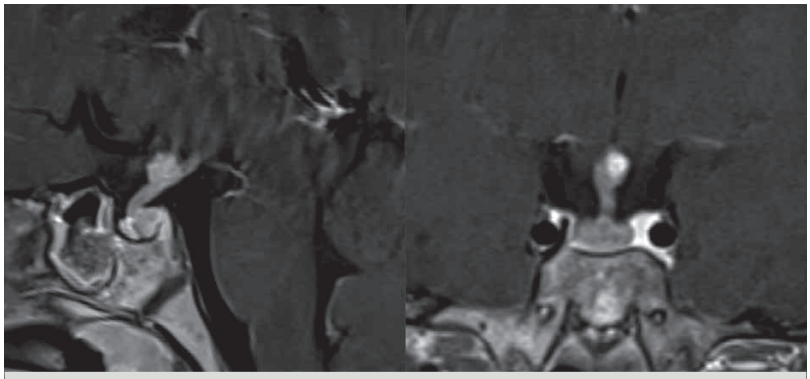


Figure 3 *Suprasellar germinoma. T1 sagittal and coronal post-contrast, showing thickening of the stalk and infundibulum.*

pituitary gland. On contrast-enhanced MRI, pituitary adenomas are often mildly hypointense compared with the normal pituitary gland, but can be isointense too. Dynamic MRI is useful for visualising microadenomas (Figure 2).[6]

Suprasellar germinomas may involve the hypothalamus, pituitary stalk and posterior pituitary gland. On CT, lesions show a high density (bright) compared with grey matter. On MRI, T1W shows isointensity compared with grey matter, while the T2W signal is variable. The tumour usually shows strong, homogenous enhancement (Figure 3). DWI often shows reduced diffusivity, suggestive of high cellularity. Frequently, the normal T1 hyperintense signal of the posterior pituitary gland is absent, differentiating it from a pituitary adenoma.[7]

> *"The pituitary gland is such a small structure that it requires specific MRI protocols to adequately assess pathologies"*

Adamantinomatous craniopharyngiomas often occur in the suprasellar region (>90%) and typically contain both cystic and solid components on MRI. The cystic component shows hyperintensity on T1W, reflecting secondary to high protein content, cholesterol, mild calcification or haemorrhage.[5] The cyst wall exhibits contrast enhancement and shows annular or nodular calcification. CT is useful for calcification detection. Oedematous changes in the brain parenchyma along the optic tract adjacent to the mass have been observed, and are considered characteristic. However, these have also been reported in pituitary adenomas, germ cell tumours and malignant lymphomas.[7]

Rayya Wael Musa Naffa',[A,B] Sivakumar Manickam[B] and Ulrike Löbel[A]

[A]*Department of Radiology, Division of Neuroradiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, and* [B]*Department of Radiology, Mid and South Essex University Hospitals NHS Trust, Basildon, UK*

References

1. Liu et al. 2023 *European Radiology* https://doi.org/10.1007/s00330-023-09585-1.
2. Mark *et al.* 2025 *American Journal of Neuroradiology* https://doi.org/10.3174/ajnr.A8596.
3. Mark *et al.* 2024 *American Journal of Neuroradiology* https://doi.org/10.3174/ajnr.A8209.
4. Mark *et al.* 2024 *American Journal of Neuroradiology* https://doi.org/10.3174/ajnr.A8171.
5. Morana & Rossi 2015 In Rossi (Ed.) *Pediatric Neuroradiology.* Berlin/Heidelberg: Springer https://doi.org/10.1007/978-3-662-46258-4_52-1.
6. Tsukamoto & Miki 2023 *Japanese Journal of Radiology* https://doi.org/10.1007/s11604-023-01400-7.
7. Tsukamoto & Miki 2023 *Japanese Journal of Radiology* https://doi.org/10.1007/s11604-023-01407-0.

Our thanks to Anita

As our long-serving President completes her term of office, we thank her for all she has done for our Society.

> *"Anita's legacy is one of passion, perseverance and progress"*

ESPE President Anita Hokken-Koelega stepped down from her role in early September, at the end of her second and final term of office. An extraordinary leader, Anita's tenure as President has been marked by her unwavering dedication, leadership, and a profound commitment to ESPE's mission.

Anita's journey with ESPE began 17 years ago. For 6 years, she served as ESPE Treasurer, where her financial expertise and meticulous attention to detail played a pivotal role in strengthening our financial foundation. Her contributions in this role were instrumental in ensuring the stability and growth of the Society.

During her 6 years as President, Anita has been a driving force behind numerous initiatives and achievements. One example was the creation of the Affiliate Society Group, which reaches paediatric endocrinologists across Europe. Another was her work on the ground-breaking EndoCompass initiative, which aims to create opportunities for the pioneers of endocrine science. Her strategic vision and ability to inspire those around her have led to significant advancements in our programmes and services. Under her leadership, we have attained new heights, expanded our reach, and made a lasting impact on the communities we serve.

Retiring President Anita Hokken-Koelega with ESPE's new President Mehul Dattani, at the Joint Congress of ESPE and ESE in May

Anita's legacy is one of passion, perseverance and progress. Her leadership has not only guided us through challenges, but has also positioned us for a future filled with promise and potential. As we reflect on her time with ESPE, we are reminded of the countless ways in which she has shaped our organisation and the lives of those we serve.

Anita's departure marks the end of an era, but her influence will continue to resonate within our Society for years to come. We extend our heartfelt thanks to Anita for her exceptional leadership and unwavering commitment. As she embarks on the next chapter of her journey, we wish her all the best and look forward to honouring her legacy in the future.

Future meetings

See **www.eurospe.org** for details of all future meetings

64th Annual ESPE Meeting
8–10 September 2026
Marseilles, France


Xantana/iStock

New ESPE Bone Academy

The ESPE Bone Academy is aimed at mid-career and senior physicians with a strong interest in paediatric bone disease. The Academy will enhance clinical skills, provide the latest scientific insights, and offer practical strategies to improve patient outcomes.

This 2-year programme of in-person and online sessions is made up of 14 modules. It starts with a 1.5-day in-person meeting in Paris, France on 24–25 February 2026 (modules 1–2).

Find out more at **www.eurospe.org/espe-bone-academy**

ESPE Bone Academy

OTHER EVENTS

ESPE–OSCAR Science Symposium
18–19 September 2025 | Paris, France

ESPE Connect Webinar: Prader–Willi Syndrome
2 October 2025 | Online

ESPE Bone Academy 2026
24–25 February 2026 | Paris, France

ESPE Winter School 2026
6–12 March 2026 | Latvia

DEADLINES

SEPTEMBER

ESPE Early Career Scientific Development Grant applications – 30 September 2025

NOVEMBER

ESPE Winter School 2026 applications – 10 November 2025

DECEMBER

ESPE Awards 2026 nominations – 10 December 2025

ESPE Research Unit Grant preliminary applications – 15 December 2025

To stay up to date, follow ESPE on social media (see right) and read the ESPE News Alerts.

For more information about vacancies on ESPE Committees and how to apply, see **www.eurospe.org/vacancies**

ESPE NEWS ARCHIVE

You will find previous newsletters in the archive at **www.eurospe.org/newsletter**

ESPE
European Society for Paediatric Endocrinology

Improving care of children with endocrine diseases by promoting knowledge and research

President
Professor Mehul Dattani
Molecular Basis of Rare Diseases Section, Genetics and Genomic Medicine Programme, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

ESPE Newsletter

Editor:
Dr Antje Garten
Pediatric Research Center
Hospital for Children and Adolescents
Leipzig University, Germany
E: Antje.Garten@medizin.uni-leipzig.de

Editorial Board:
Dr Rakesh Kumar
(Chandigarh, India)
Dr Ruta Navardauskaite
(Kaunas, Lithuania)
Dr Divya Pujari
(Mumbai, India)
Dr Meera Shaunak
(London, UK)
Dr Chris Worth
(Manchester, UK)

Sub-Editor:
Caroline Brewser

Designed by:
Ian Atherton
E: corbiculadesign@gmail.com

Published by:
MCI Benelux SA
Avenue des Arts 47
1000 Brussels, Belgium
W: www.eurospe.org

ESPE Office
MCI Benelux (address above) manages the ESPE Office.

Interplan is the Professional Congress Organiser (PCO) for the ESPE Annual Meetings

ESPE Managers:
Charlotta Odlind and Teresa Cunha

ESPE Enquiries:
General
E: secretariat@eurospe.org
Membership
E: membershipESPE@eurospe.org
W: www.eurospe.org

www.facebook.com/EuroSPE
www.instagram.com/espe_endocrinology
www.x.com/EuroSPE
www.linkedin.com/company/european-society-for-paediatric-endocrinology

ESPE e-Learning
Answer to the case query on **page 3**

The correct answer is magnetic resonance imaging (MRI).

In patients with hypogonadotrophic hypogonadism, imaging of the hypothalamo-pituitary region is essential, to exclude mass lesions.

In the case of Kallmann syndrome, additional images specific to the visualisation of the olfactory bulb and sulci are indicated. MRI appears to be superior to computed tomography in detecting mass lesions and developmental abnormalities of the hypothalamo-pituitary region.